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10/601,072	06/19/2003	Jean-Philippe Girard	ENDOC.009CP1	5184

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/601,072	GIRARD ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17-22,24-28 and 92-121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17-22,24-28 and 92-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/18/2007*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

The request filed on 10/30/2007 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10601072 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 1-14, 16, 23, 29-91 have been cancelled.

Claims 99-121 are added.

Claims 15, 17-22, 24-28, 92-121 are pending and examined on the merits for the method of binding or inhibiting the activity of chemokine (elect CCL5 and search an additional species, SLC/CCL21) comprising contacting the chemokine with the polypeptide of SEQ ID NO:3 or its fragments or variants.

Priority

The Office has established the effective priority dated of June 19, 2003, the filing dated of the instant application as set forth in the previous Office Action dated 7/27/2006.

Claim Objection

1. Claim 21, 22, 93, 94, 106, 107, 114, and 115 are objected to because of the following informalities: The term SLC is an abbreviation of Secondary Lymphoid-Tissue Chemokine (See Mesh Word, NCBI, attached). The abbreviation SLC should be spelled out when first used in the claims. Appropriate correction is required.

2. Claims 18, 19, 103, and 104 are objected to because of the following informalities: The specification teaches THAP as THanatos (death)-Associated Protein (abstract). The abbreviation THAP should be spelled out when first used in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of **the first paragraph of 35 U.S.C. 112**:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection- *A method drawn to a variant of SEQ ID NO: 3 or the chemokine binding domain (143-213 of SEQ ID NO: 3)*

Claims 15, 17-22, 24-28, 92-121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The specification must describe the claimed invention in sufficient detail for the claimed invention comprising the process and genus of the products used in the process. Possession may be shown, for example, by describing an actual reduction to practice of the claimed invention. A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose.

In this case the claims are broadly drawn to a method of binding or inhibiting a activity of a chemokine comprising contacting to a chemokine (any chemokine) comprising SLC/CCL21 and CCL5 with a THAP1 polypeptide comprising the full length of SEQ ID NO: 3, chemokine binding domain (143-213 of SEQ ID NO: 3) or its homologies (95% or more sequence identity). Thus, the claims are inclusive of variant polypeptides that are 95% identical to the amino acids of SEQ ID NO: 3 or the domain of 143-213 of SEQ ID NO: 3 in the method for binding or inhibiting an activity of a chemokine by contacting to any of the known chemokines.

The figure 12 of the specification describes the polypeptide fragments of THAP1 (SEQ ID NO: 3) and the chemokine-binding domain of THAP1 (143-213 of SEQ ID NO: 3) associated with the chemokine SLC-binding. The figure 19, teaches that the THAP1-GST fusion protein binds to a few more chemokines comprising CCL5 and SLC. The specification does not provide teaching on **A)** any activity or function of a

chemokine is inhibited upon the binding by the peptide of THAP1 or its variants having 95% identity to the THAP1 of SEQ ID NO: 3 or the chemokine binding domain; **B)** the structure of the known chemokines involved in the binding to the THAP1 of SEQ ID NO: 3, the binding domain (143-213 of SEQ ID NO: 3) or its variants.

Regarding to the binding of a chemokine to the variants of THAP1 having 95% identity to the THAP1 of SEQ ID NO: 3 or the chemokine binding domain, the figure 12 of the specification although provides C-terminal fragments of THAP1, as a chemokine binding domain (143-213 amino acids of SEQ ID NO: 3) being responsible for the SLC/CCL21 binding, the full length THAP1 (213 amino acids) with a deletion of five amino acids at position 168-172, ΔQRCRR in the binding domain, which counts more than 95% sequence identity to SEQ ID NO: 3, shows no binding activity. Thus, the specification self has suggested that not all the polypeptide having more than 95% identity to the sequence of SEQ ID NO: 3 has the binding ability to the chemokine, SLC/CCL21.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics. i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613.

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The specification provides neither a representative number of polypeptides that encompass the genus that reveal the roles of these polypeptides in the binding and inhibition of the activity of any chemokine, nor does it provide a description of structural features that are common to the polypeptide having at least 95% homology to amino acid sequence 143-213 of SEQ ID NO: 3 that could inhibit any activity of any chemokine including CCL5 and SLC. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of the species of polypeptide is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the applicants, at time of filing the application, do not have the possession of claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) and functional attribute(s) of the encompassed genus of polypeptides or the chemokines, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the THAP1 protein of SEQ ID NO: 3, and the chemokine binding domain of 143-213 of SEQ ID NO: 3 that bind to SLC/CCL21 and inhibit the activity of CCL5/RANTES (set forth in the declaration of co-inventor, Jean-Philippe Girard), but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In the remarks filed with this RCE, applicant states that the claims have been amended to overcome the rejection made before. It is noted that the Written Description rejection above is reformed for the newly amended claims.

Scope of Enablement rejection *-A method drawn to inhibiting any chemokine activity by a variant of SEQ ID NO: 3 or the chemokine binding domain (143-213 of SEQ ID NO: 3)*

Claims 15, 17-22, 24-28, and 92-121 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the CCL5 chemokine activity by contacting the THAP1 protein of SEQ ID NO: 3 (full length) or its chemokine binding domain (143-213 of SEQ ID NO: 3) and a method of binding the THAP1 protein of SEQ ID NO: 3 (full length) or its chemokine binding domain (143-213 of SEQ ID NO: 3) to the chemokines of SLC/CCL21 and CCL5 , does not reasonably provide enablement for **A)** the method of inhibiting an activity of the other chemokines with any form of THAP1 protein comprising the full length of SEQ ID NO: 3, chemokine binding domain (143-213 of SEQ ID NO: 3) or its homologies (95% or more sequence identity) and **B)** the method of inhibiting the activity of any chemokine including SLC/CCL21 or CCL5 by contacting and binding the THAP1 homologies having at least 95% sequence identity to SEQ ID NO: 3 or to the chemokine binding domain (143-213 of SEQ ID NO:3).

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a method of inhibiting the activity of a (any) chemokine comprising contacting or binding a chemokine with an agent comprising polypeptides having at least 95% amino acid identity to chemokine-binding domain of amino acid residues 143-213 of SEQ ID NO: 3, wherein the activity of said chemokine is inhibited. However, the specification, on page 230 (example 15-17) only teaches THAP1 protein of SEQ ID NO: 3 and the chemokine binding domain (143-213 of SEQ ID NO: 3) that is able to bind to a chemokine SLC/CCL21 or CCL5. The specification on page 252-259 (example 32-37) lists many chemokines being tested and figure 19 teaches the result that only few of the chemokines are bound to the THAP1 of SEQ ID NO: 3. The specification does not provided **A)** any teaching, direction/guideline, working example, or experimentation to show that any other chemokines binding to the THAP1 protein or polypeptides of SEQ ID NO: 3 result in an inhibition of the activity or the function of the chemokines; **B)** inhibiting the activity of any chemokine including SLC/CCL21 or CCL5 by contacting and binding to the THAP1 homologies having 95% sequence identity to SEQ ID NO: 3 or to the chemokine binding domain (143-213 of SEQ ID NO:3). The figures 19 and 20 showing the GST-THAP1 in vitro binding to few of the CC and CXC chemokines does not convince one skilled in the art that the THAP1 protein could bind to all the CC and CXC chemokines. The description of the chemokine binding domain (143-213 of SEQ ID NO: 3) THAP1 with N-terminus deletion (figure 12) binding to SLC/CCL21 does not suggest that those deleted fragments could bind to any other chemokine to inhibit their functions. In term of the peptide having at least 95% identity to a SEQ ID NO: 3 or the chemokine binding domain, instant specification in figure 12 also teaches that the full length THAP1 (213 amino acids) with a deletion of five amino acids at position 168-172, ΔQRCRR, which counts less than 5% the amino acid difference compared to SEQ ID NO: 3, does not have the binding ability to SLC. Thus, the specification self has suggested that not all the peptides that are more than 95% identity to SEQ ID NO: 3 have the binding capacity to the SLC. Thus, the specification fails to provide enablement disclosure for claimed invention which one skilled in the art could use the invention without undue a quantity of experimentations.

It is also know in the art that even a single modification or substitution in a protein sequence can alter the protein function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al, Journal of Cell biology, Vol 111, p2129-2138, 1990, provided in the Office Action 07/27/2006). Removal of the amino terminal histidine of glucagons substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin et al Biochemistry USA, vol 14, p1559-1563, 1975, provided in the Office Action 07/27/2006). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

In view of the lack of guidance, lack of examples, and lack of predictability and objective evidence showing that the THAP1 of SEQ ID NO: 3 or the chemokine binding domain could bind to any chemokine or a chemokine with defined the structure and showing any peptide having 95% the sequence identity to the SEQ ID NO: 3 or the binding domain having binding or inhibiting ability to a chemokine activity, one skilled in the art would not know how to use the claimed invention based on the teachings in the prior art or instant specification and under a quantity of experimentations would be forced.

Previous response to applicant's argument dated 1/29/2007 is also maintained for the reason of record as set forth in the Office Action dated 04/27/2007.

Response to applicant's argument in the remarks and declaration by Dr. JP Girard dated 10/30/2007.

The response has been carefully considered but is deemed not to be persuasive to overcome the current rejection set forth above. In remarks applicant states:

> a Declaration under 37 C.F.R. § 1.132 of co-inventor Dr. Jean-Philippe Girard, which shows that amended claim 15 is fully enabled. In particular, as stated in item 5 of the declaration, both in vitro and in vivo experiments to determine inhibition of chemokine activity were preformed using the chemokine-binding domain of SEQ ID NO: 3 and pro-inflammatory chemokines.

and then, applicant presents experimentations disclosed in the recent filed application (11360450, filed on 2/22/2006) showing that the chemotaxis activities of the chemokine, CCL5/RANTES, are inhibited in the

presence of THAP1 protein or the chemokine binding domain by in vitro and in vivo assays. In response, the declaration dated 10/30/2007 under 37 CFR 1.131 has been considered and entered. The office considers that the declaration provides evidence showing that the activity of CCL5 is inhibited by THAP1 and its chemokine binding domain, which has been contemplated in the specification and the binding of CCL5 to THAP1 in figure 19. However the declaration is insufficient to overcome the rejection for the claims drawn to a method of inhibiting a (any) activity of a (any) chemokine by contacting the THAP1 of SEQ ID NO: 3 or the chemokine binding domain and inhibiting the activity of a chemokine by the peptide having at least 95% sequence identity to SEQ ID NO: 3 or its chemokine binding domain (143-213 of SEQ ID NO: 3) because the declaration does not show such peptides or variants having claimed function and does not show any THAP1 protein or peptide comprising the wild type, full length, or chemokine binding domain of the THAP1 having function for inhibiting the activities, such as chemotaxis or cell recruitment by other chemokine except CCL5. Showing one chemokine, CCL5, would not represent other chemokines because each chemokine has the unique structure and functional role in different cells and different normal or pathological conditions. Thus, applicant's argument and declaration have not been found persuasive to overcome the entirety of the rejection, and therefore the scope of enablement rejection is reformed as above.

Conclusion

No claims are allowed. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tang et al., (WO200157190, 8/9/2001) teach proteins or fragments of proteins that may be involved in chemotactic or chemokinetic activity for mammalian cells, including, lymphocyte chemotactic proteins (section 4. 10. 9, page 52+). Tang et al., teach a specific protein (SEQ ID NO: 1928) that is 100% identical to the full length sequence of THAP1 (SEQ ID NO: 3) comprising the chemokine binding domain (143-213 of SEQ ID NO: 3). Tang et al., although suggest that the genus of the polypeptides and proteins disclosed may be involved in chemotactic or chemokinetic activity for mammalian cells (section 4. 10. 9), **no** method step, example, or experimentation are disclosed. Tang et al., do not teach or

suggest a method of inhibiting the activity of chemokine by any of the disclosed protein or its fragments comprising the steps of contacting or binding the chemokines comprising SCL and CCL5.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER